[redacted]: This material may be protected by copyright law.

(23)

Acta psychiat. scand. (1983) 67, Suppl. 303, 26—37

Department of Psychiatry Children's Hospital Medical Center Harvard Medical School (Head: Prof. *J. Richmond*) Boston, Massachusetts, U.S.A.

Lead at low dose and the behavior of children

H. L. NEEDLEMAN

Over 3,000 children attending first and second grade in public school were classified as to past lead exposure according to the concentrations of lead in their teeth. Those in the highest and lowest deciles for lead were evaluated by a broad panel of neuropsychologic outcome measures. Controlled either by matching or analysis of coveriance were 39 other variables which could effect outcome. High lead children were significantly impaired on IQ, auditory processing and reaction time under varying intervals of delay. Teacher's rating scales showed a dose-related increase in non-adaptive classroom behavior with no evidence of a threshold. EEG scores and observations of children in class demonstrated differences in high and low lead subjects.

Key words: lead intoxication — IQ scores — teacher's rating scales — electroencephalograms — epidemiology — learning disabilities.

This symposium's title inquires whether the effects of environmental neurotoxins on psychiatric status are a new problem, and this meeting is probably the first to give formal recognition to the premise that such agents, because they alter mood and thought, are proper candidates for psychiatric study. At the same time, it is somewhat humbling to note that Dioscorides, in the first century A. D., recognized this issue and foreshadowed us when he wrote of the effects of one environmental neurotoxin, lead, that "the mind gives way; the limbs are paralyzed".

Lead is the best and longest studied of the neurotoxins. It can be a useful paradigm with which to deepen our understanding of the health significance of hazardous substances in general and to clarify the necessary steps and barriers to their removal from the human environment.

The recognition of a neurotoxin usually begins with the identification of often dramatic high dose effects, generally encountered in the work place. Following this, community high dose exposures due to industrial spills or accidents are recognized. As knowledge of the biochemical toxicology of a toxin broadens, more sensitive measures of toxicity are developed, and the threshold for effect is revised accordingly downward. Vulnerable segments of the population are then identified, and the question of whether ordinary community exposures are toxic is raised. Epidemiological and experimental studies are then conducted to define the extent of the problem and to elaborate potential toxic mechanisms.

Scientific understanding of lead toxicity has followed this course. Initially, lead intoxication was recognized as a disease only of miners, smelters and painters. In the mid-18th century, *Sir George Baker* demonstrated that the endemic colic in Devonshire came from lead introduced into the local cider during the grinding of apples. At about

the same time, rum made in Massachusetts and exported to North Carolina was found to contain lead and to be responsible for the "dry gripes" which afflicted consumers of liquor in the South. This resulted in one of the first public health laws in the Colonies, banning the use of lead tubing or containers in distilling liquor.

Childhood lead poisoning was first identified at the turn of this century. In the United States, it has been considered a disease almost exclusively of poor minorities living in deteriorated leaded housing. Children who recovered from lead poisoning were formerly thought to be unmarked by the disease after recovery. *Byers & Lord* (1943) followed a group of twenty "recovered" children into their school years and found that nineteen were failing in school, had attentional deficits or behavior disorders. They noted that most of the cases they followed would ordinarily not be recognized. For the first time, the question of unidentified lead intoxication as a cause of enduring neurobehavioral disorder was raised.

In the 1960's and 1970's, screening surveys of children in the United States demonstrated that in certain areas, between 6 % and 10 % of asymptomatic children had blood lead levels greater than 40 μg/dl — considered at that time the lower bound for undue exposure. A number of studies were conducted which attempted to determine whether exposure to doses of lead below those which produced stark symptoms was associated with neurobehavioral deficits.

In this paper, I shall focus on the studies conducted by my group over the past six years. In these studies we tested the hypothesis that children exposed to lead who did not have clinical symptoms would, nevertheless, perform inferiorly to non-exposed controls in a number of psychological dimensions.

Most previous studies of this question were flawed to greater or lesser extent by inadequate attention to these four methodological problems:

(1) *Poor Markers of Earlier Lead Exposure* — Most studies relied on blood lead to classify exposure. Since blood lead is a short-term marker, it may return to normal after a child has stopped taking in large quantities of the metal. Blood leads may be normal, then when tissue leads are high.

(2) *Insensitive Measures of Outcome* — Group tests, or screening tests of developmental function, cannot be used to detect small amounts of change.

(3) *Inadequate Attention to Non-lead Variables Which Could Confound the Effect of Lead on Outcome* — Socioeconomic status, parental rearing style, parental intelligence and medical history are among the variables which could be associated with lead exposure and outcome. Identification and control of these and other covariates are necessary to measure the effects of lead.

(4) *Selection Bias* — Subjects who enter a study may differ in a systematic fashion from those who reject participation. Some estimate of the extent and effect of bias on the relationship between the independent and dependent variables under examination should be attempted.

INVESTIGATIONS

A. A study of neurobehavioral outcome

In 1975, we collected teeth from over 3,000 first and second grade children attending ordinary, non-remedial classes. The population sampled lived in two primarily white, working class towns adjacent to Boston, Massachusetts. Previously, teeth had been

REPRODUCED AT GOVERNMENT EXPENSE

shown to accurately mark past expouse to lead (*Needleman et al.* (1974)) well after exposure had ended. The distribution of dentine lead levels, measured by anodic stripping voltammetry was log normal (*Needleman et al.* (1979)). Children who hade two concordant dentine lead levels which placed them in the tenth percentile (low lead group) or the ninetieth percentile (high lead group) (<10 ppm or >20 ppm, respectively) were invited to participate in the neuropsychological followup study. Children were accepted if they had been born at term, had no significant head injuries or neurologic diseases, had never been known to have excess lead exposure, and if English was the first language at home. To evaluate selection bias, we compared participant and non-paritcipant children on distribution of lead levels and teacher ratings on an eleven-item classroom behavior scale. Included subjects did not differ from excluded subjects in either dimension.

While the child was being tested, the mother filled out a lengthy questionnaire evaluating 39 non-lead convariates. She also took a brief IQ test. When high and low lead subjects were compared on these covariates only 5 differed at $P<0.1$ or less. A partial list of covariates is displayed in Table 1. The subjects were given an extensive neurobehavioral assessment battery in fixed order by psychometricians who were blind to the dentine levels. The areas of performance evaluated were: Intelligence (WISC-R); Concrete operational intelligence (Piagetian conservation of number, substance comprehension and achievement tests): Auditory and language processing (Token Test, Seas-

Table 1: *Comparision of Non-Lead Variables in High and Low Lead Groups*

Variable	*Low Dentine Lead*	*High Dentine Lead*	*P Value*
General			
% Male	49.5	55.9	NS
% White	97.0	98.3	NS
% Father Head of Household	77.2	67.8	NS
% Positive Pica	10.9	28.8	0.008
Physical Variables			
Age (mo)	87.2 ± 7.7	90.7 ± 8.4	0.009
Height (cm)	126.6 ± 6.3	126.4 ± 6.3	NS
Weight (kg)	25.8 ± 4.9	26.5 ± 4.6	NS
Head Circumference	51.8 ± 1.6	51.7 ± 1.5	NS
Pas Medical History			
Birth Weight (gm)	3400.00 ± 448.6	3346.0 ± 514.0	NS
No. of hospital Admissions	0.47 ± 1.2	0.42 ± 1.6	NS
Parental Variables			
No. of Pregnancies	3.3 ± 1.8	3.8 ± 2.3	0.10
Mother's age at subjects birth (yr)	26.2 ± 5.5	24.5 ± 5.8	0.07
Mother's social class	4.1 ± 0.8	4.2 ± 0.8	NS
Mother's education (grade)	11.9 ± 2.0	11.4 ± 1.7	0.08
Father's social class	3.8 ± 1.0	4.1 ± 0.8	0.02
Parent IQ	111.8 ± 14.0	108.7 ± 14.5	NS

REPRODUCED AT GOVERNMENT EXPENSE

Table 2: *Teacher's Behavioral Rating Scale*

1. Is this child easily distracted during his/her work?
2. Can he/she persist with a task for a reasonable amount of time?
3. Can this child work independently and complete assigned tasks with minimal assistance?
4. Is his/her approach to tasks disorganized (constantly miplacing pencils, books, etc.)?
5. Do you consider this child hyperactive?
6. Is he/she over-excitable and impulsive?
7. Is he/she easily frustrated by difficulties?
8. Is he/she a daydreamer?
9. Can he/she follow simple directions?
10. Can he/she follow a sequence of directions?
11. In general, is this child functioning as well in the classroom as other children his/her own age?

hore Rhythm Test and Wepman Auditory Discrimination Test); Visual motor coordination (VMI and Frostig); Attentional performance (Reaction time under varying intervals of delay); Motor coordination (Elements of Halstead-Reitan Battery).

We attempted to secure a teacher's rating on each child who gave a tooth. The instrument employed was an eleven item, forced-choice questionnaire (Table 2).

In the data analysis, we employed analysis of covariance, with lead as the main effect. Those five variables which on t-test differed by $P<0.1$ were entered into the model and controlled. They were: Mother's age at subject's birth, mother's education, family size, father's socioeconomic status and parental IQ.

For all the outcome measures evaluated, the low lead group's performance was favored except for one item. For brevity's sake, only those tests where the P value was <0.05 are tabulated here (Table 3 & 4). Lead is seen to be associated with deficits in IQ, verbal IQ, auditory processing and reaction time under varying intervals of delay. Teachers rated high level subjects over twice as frequently negative on each item evaluated.

In addition, we cross-tabulated all 2146 children on whom we had a teacher's rating scale and at least one dentine lead level. The subjects were classified into six groups according to dentine lead level, and the percentage of negative reports for each item calculated (*Fig.* 1). A regular relationship between dentine lead level and proportion of negtively rated children was found.

B. Electroencephalographic effects

Burchfiel et al. (1980) then took a randomly chosen subsample of the subjects tested above (19 high lead, 22 low lead). Each child received a standard 20-channel EEG under four conditions: eyes open, eyes closed, during hyperventilation, and post hyperventilation. Four bandwidths were examined: delta (0.5—3.5 Hz), theta (4.0—7.5 Hz), alpha (8—12 Hz), and beta (12.5—31.5 Hz). Spectral energy was summed within each bandwidth and the results expressed as a percentage of total energy over the range of 0.5—32 Hz.

When the proportion of spectral energy in each band was compared for high and low lead subjects by univariate techniques (*Mann-Whitney* two-sample ranks test), high lead subjects were found to have higher proportions of delta in the central, parietal and occipital regions bilaterally. High lead subjects also had less alpha in the occipital and midline central parietal regions (Fig. 2 & 3).

REPRODUCED AT GOVERNMENT EXPENSE

Table 3: *Comparison of Outcomes on the Wechsler Intelligence Scale for Children (Revised) Between High and Low Lead Subjects (Analysis of Covariance)*

	Low Lead (Mean)	*High Lead (Mean)*	*P Value*
Full Scale IQ	106.6	102.1	0.03
Verbal IQ	103.9	99.3	0.03
Information	10.5	9.4	0.04
Vocabulary	11.0	10.0	0.05
Digit Span	10.6	9.3	0.02
Arithmetic	10.4	10.1	0.49
Comprehension	11.0	10.2	0.08
Similarities	10.8	10.3	0.36
Performance IQ	108.7	104.9	0.08
Picture Completion	12.2	11.3	0.03
Picture Arrangement	11.3	10.8	0.38
Block Design	11.0	10.3	0.15
Object Assembly	10.9	10.6	0.54
Coding	11.0	10.9	0.90
Mazes	10.6	10.1	0.37

Table 4. *Comparison of Auditory Processing Scores and Reaction Time Under Varying Delay Between High and Low Lead Subjetcs*

Test	*Low Lead* (Mean)	*High Lead* (Mean)	*P Value*
Seashore Rhytm Test			
Subtest A	8.2	7.1	0.002
Subtest B	7.5	6.8	0.03
Subtest C	6.0	5.4	0.07
Sum	21.6	19.4	0.002
Token Test			
Block 1	2.9	2.8	0.37
Block 2	3.7	3.7	0.90
Block 3	4.1	4.0	0.42
Block 4	14.1	13.1	0.05
Sum	24.8	23.6	0.09
Sentence Repetition Test	12.6	11.3	0.04
Reaction Time Under Varying Intervals of Delay			
Block 1 (3 sec)	0.35±0.08	0.37±0.09	0.32
Block 2 (12 sec)	0.41±0.09	0.47±0.12	0.001
Block 3 (12 sec)	0.41±0.09	0.48±0.11	0.001
Block 4 (3 sec)	0.38±0.10	0.41±0.12	0.01

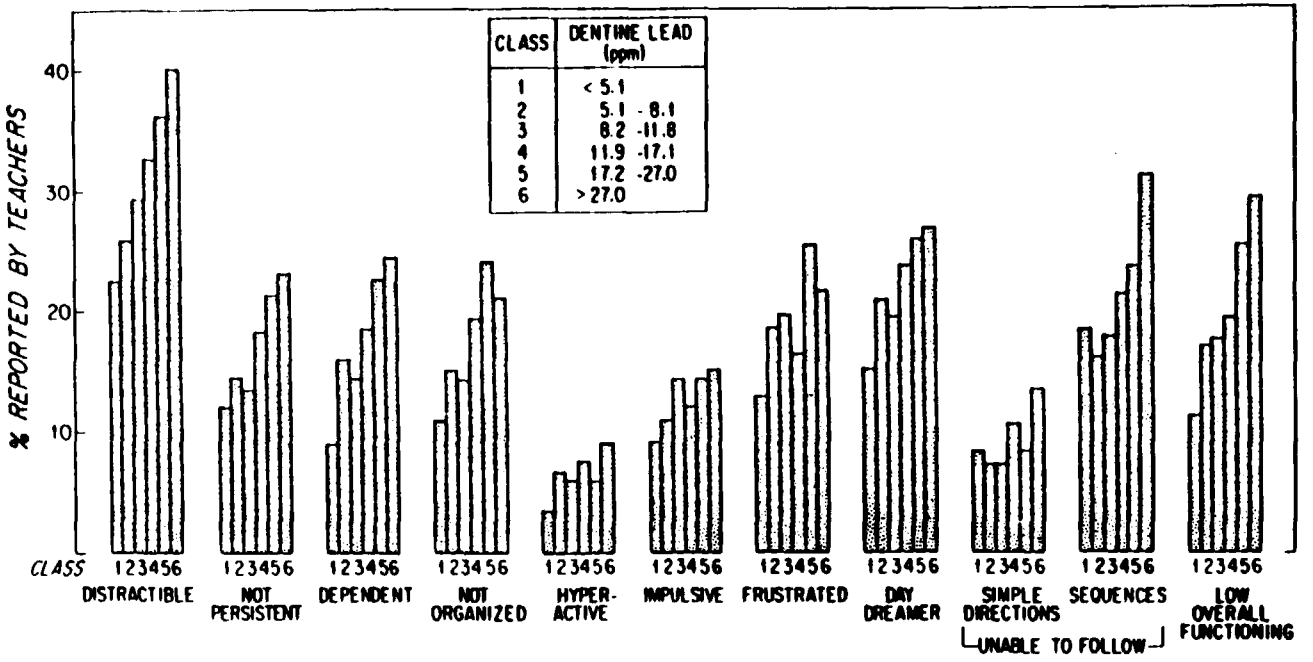

Fig 1. Distribution of negative teacher's ratings in children classified by dentine lead level ($N = 2146$). The groups were bounded in order to achieve symmetrical distribution of subjects in each cell around the median. (Reprinted with permission from *Needleman et al.* (1979)).

REPRODUCED AT GOVERNMENT EXPENSE

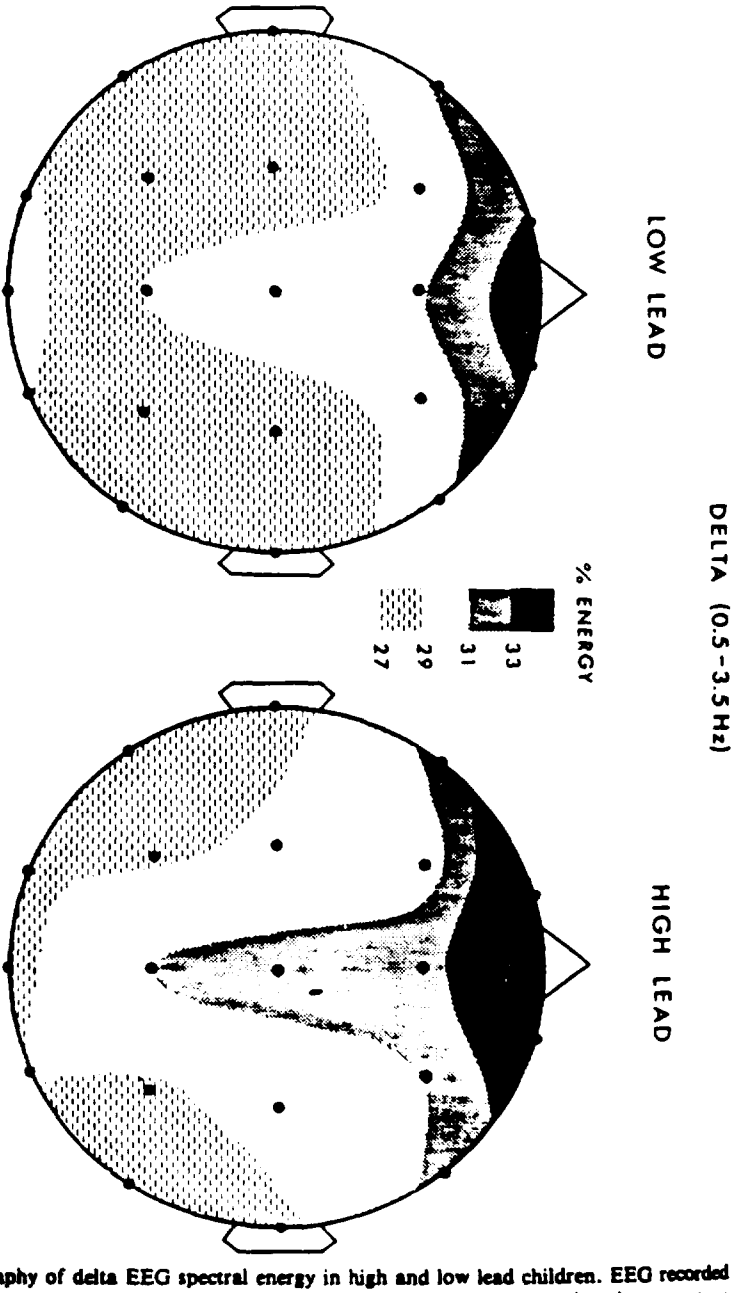

Fig 2. Topography of delta EEG spectral energy in high and low lead children. EEG recorded while subjects were relaxed, alert with eyes closed. Delta energy was calculated as the percentage of EEG spectral energy in the frequency range 0.5—3.5 Hz. This was done for each electrode derivation from the mean EEG spectrum of the high and low lead group, respectively, and topographical maps of delta energy were constructed by linear interpolation based upon the values of the nearest 3 electrode points (11). (Reprinted with permission from *Burchfiel et al.* (1980)).

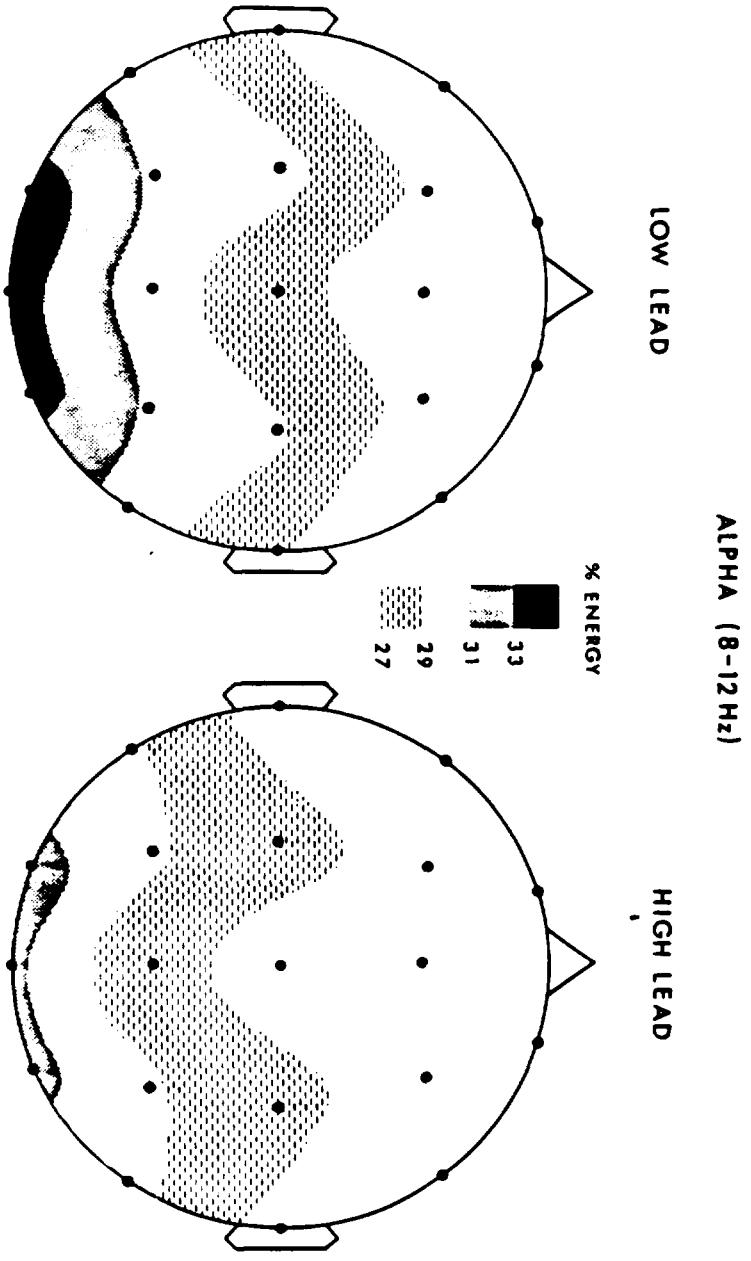

Fig 3. Topography of alpha (8—12 Hz) EEG spectral energy in high and low lead children. Same recording condition as in Figure 2. See legend of Figure 2 for further details. (Reprinted with permission from *Burchfiel et al.* (1980)).

REPRODUCED AT GOVERNMENT EXPENSE

Table 5. *Classification of Subjects Based On Stepwise Discriminant Analysis.*

Features	*Percentage of Subjects Correctly Classified* *Low Lead*	*High Lead*	*All*
EEG	68.2 %	73.7 %	70.7 %
Psychologic	72.7	63.2	68.3
EEG & Psychologic	77.3	73.7	75.6

Table 6. *Percentage of Intervals in Which Off-Task Behavior Was Observed.*

Behavior	*Dentine Lead Level* *High*	*Middle*	*Low*
Out of Seat	0.8±1.4	0.7±1.7	0.3±0.7
Glances at Peer	9.3±7.4	6.0±2.8	6.5±2.4
Glances at Group	6.8±12.8	4.6±4.5	4.1±5.3
Glances at Observer	10.1±4.0	7.4±6.1	5.6±3.3
Glances at Desk	5.5±8.0	1.7±2.0	3.9±8.5
Glances Away	4.2±3.1	2.4±2.3	2.2±1.9
Peer Interaction	12.0±8.1	8.0±8.1	7.9±8.4

When the EEG features were combined with nine of the previously obtained psychologic outcome variables and parent IQ and then entered into a stepwise discriminant analysis, a combination of EEG features and psychological features increased the discriminating power over that of either set of variables (Table 5).

C. School Performance

Bellinger et al. (1981), blind to the tooth lead levels of the children, observed the classroom behavior of 15 low-lead, 13 mid-lead and 13 high-lead children three years after the initial study was completed. Children were observed at quiet academic activity for four, four-minute epochs. At seven-second intervals their behavior was scored as on or off task. Table 6 indicates the percentage of intervals spent in off-task behavior. A dose-response relationship between earlier dentine lead level and amount of off-task behavior is seen.

DISCUSSION:

Controlling for covariates which differ between groups, high lead subjects are deficient in IQ, auditory processing, attention and display more disordered classroom behavior. Their EEG's differ from their low lead counterparts, particularly in midline structures. High lead subjects, three years after the initial study, spend more time in distracted, off-task activity, looking at peers, at the observer, or away from their work.

Among the frequent questions evoked by this work are these: Is it not possible that *pica* is a marker of disordered behavior and that disordered children eat more lead? What is the real significance of a mean difference between groups of 4.5 points on the IQ? Is this really worth bothering about?

Table 7. *Teachers Ratings Stratified by Dentine Lead Level and Presence of Pica.*

Presence of Pica	*Dentine Lead Level*			
	Low		*High*	
$N_{tot} = 154$	$N = 97$	$\bar{x}$	$N = 57$	$\bar{x}$
Yes	10	7.9 ± 3.8	15	8.7 ± 2.9
No	87	9.8 ± 2.3	42	7.4 ± 3.9

			t	P
Low Dentine Pb 9.6±2.6*	vs.	High Dentine Pb 7.7±3.7*	3.78	<0.001
No Pica 9.0±3.1*	vs.	Pica 8.4±3.2*	0.93	0.17

* Values are sum scores of teachers ratings (0 = bad; 11 = good)

Table 7 demonstrates that when children are stratified as to the presence or absence of *pica* and their lead burden, poor performance on teacher's rating is not associated with *pica*, but is associated with lead burden. Figure 4 plots the actual cumulative frequency distributions of verbal IQ scores before covarying the five control variables. It is apparent that while the group medians are only six points apart, the percentage of high lead children with deficient (<75) IQ scores is three times that in the low lead group. The shaded areas indicate that while no low lead children have verbal IQ scores below 66, 4.8% of high lead children have scores below 66. At the upper end of the distribution, no high lead child has an IQ score greater than 125, while 4% of low lead children are above this boundary.

Studies of schoolage children, using dentine lead as a marker (*Winneke* 1981)) have also shown decreased IQ scores in high lead subjects. In a more recent paper (*Winneke* 1982)) the authors found that parents' ratings of children's behavior and visual motor integration were impaired in leaded children.

Yule et al. (1981) showed IQ deficits, reading and spelling in children with blood lead levels >13 *mg*/dl when compared with children with blood leads <13 *mg*/dl controlling for socioeconomic status and sex. *Landsdown et al.* (1982) employing the same teacher's rating scale in London children found strikingly similar results.

Cowan and *Leviton* calculated attributable risk for inferior classroom performance by the following formula:

$$\textit{Attributable Risk} = \frac{I_E - I_O}{I_E}(AR) = \frac{.26 - .14}{.26} = 0.69$$

where

I_E = incidence in exposed group, I_O = incidence in unexposed group

Sixty-nine percent of these children with elevated dentine lead levels had inferior classroom performance associated with their lead exposure.

REPRODUCED AT GOVERNMENT EXPENSE

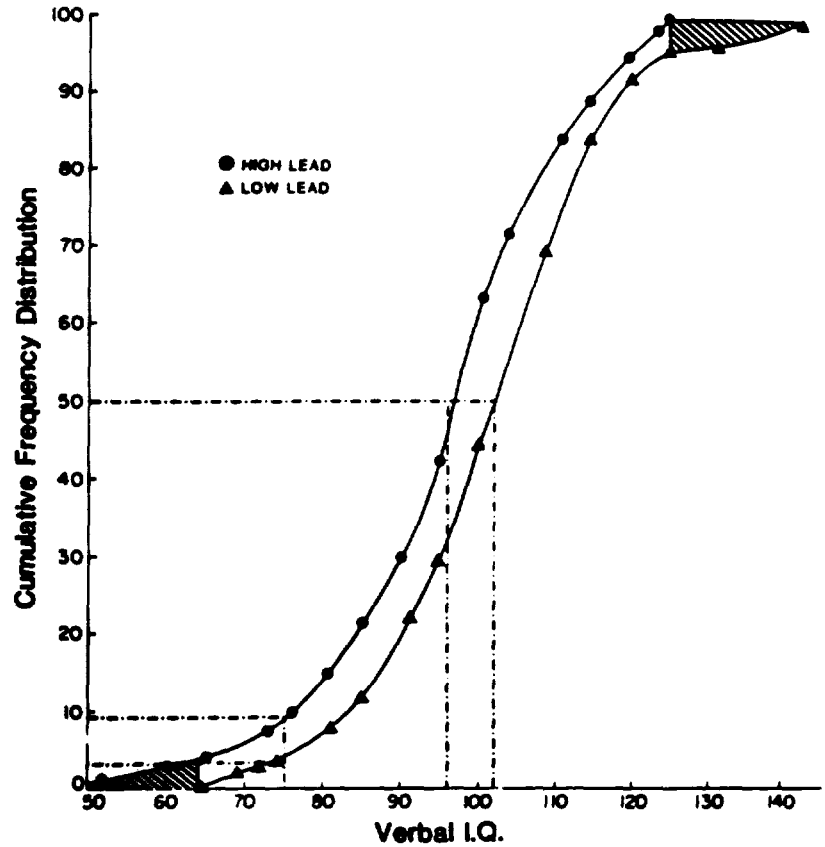

Fig 4. Cumulative frequency distribution of verbal IQ scores in high and low lead subjects.

These epidemiologic data demonstrate a clear effect of lead at low dose. When taken with animal studies which show disturbed learning at low dose in the rodent (*Petit & Alfano* (1979)) and non-human primate (*Bushnell & Bowman* (1979)), altered development of synapses in the developing rodent brain (*Averill & Needleman* (1980)) and delayed appearance of brain cytochromes in the immature rodent (*Bull et al.* (1979)), the case seems strong indeed that lead at low is an important and widely distributed neurotoxin.

Unlike many neuropsychiatric deseases, an enormous amount is known about lead poisoning. The etiology, some of the biochemical toxicology, and the necessary steps to eliminate the problem are clearly spelled out. The larger challenges with lead lie in finding the will and means to remove it from the human environment.

ACKNOWLEDGEMENTS

This work was supported by grants from the National Institute of Child Health and Human Development and from the U.S. Environmental Protection Agency.

REFERENCES

Averill, D. A., & H. L. Needleman (1980): Neonatal lead exposure retards cortical synaptogenesis in the rat. In *Needleman, H. L.* (ed): Low Level Lead Exposure: The Clinical Implications of Current Research. Raven Press, New York, pp. 201—210.

Bellinger, D., H. Needleman, J. Hargrave & M. Nichols (1981): Elevated dentine lead levels and school success. Proc. Biennial Meeting Soc. Res. Child Dev.

Bull, R. J., Lutkenhoff, S. D., G. E. McCarty & R. G. Miller (1979): Delays in the postnatal increase of cerebral cytochrome concentrations in lead-exposed rats. Neuropharmacol *18*, 83.

Burchfiel, J., F. Duffy & P. H. Bartels (1980): Combined discriminating power of quantitative electroencepahlography and neuropsychologic measures in evaluting CNS effects of lead at low levels. In *Needleman, H. L.* (ed): Low Level Lead Exposure: The Clinical Implications of Current Research, Raven Press, New York, pp. 75—90.

Bushnell, P. J., & R. E. Bowman (1979): Reversal learning deficits in young monkeys exposed to lead. Pharmacol. Biochem. & Behav. *10*, 33.

Byers, R. K., & E. E. Lord (1943): Late effects of lead poisoning on mental development. Am. J. Dis. Child. *66*, 471.

Lansdown, R., Yule, W., M. A. Urbanowicz & I. B. Millar (1982): Reltionships between blood lead, intelligence and behavior in children: Overview of a pilot study. In *Rutter, M.* (ed): Low Level Lead Exposure and Its Effect on Human Beings, John Wiley, New York.

Needleman, H. L., I. Davidson, I. M. Shapiro & E. Sewell (1974): Subclinical lead exposure in Philadelphia school children: Identification by dentine lead anaLysis. N. Engl. J. Med. *290*, 245.

Needleman, H. L., C. G. Gunnoe & A. Leviton, R. Reed, H. Peresie, C. Maher & A. Burrett (1979): Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N. Engl. J. Med. *300*, 689.

Petit, T. L. & D. P. Alfano (1979): Differential experience following lead exposure: Effects on brain and behavior. Pharmacol. Biochem. & Behav. *11*, 165.

Winneke G., Brockhaus, A., Kramer, U., Ewers, U., Kujanek, G., H. Lechner & W. Janke (1981): Neuropsychological comparison of children with different tooth lead levels. Proc. Int. Conf. Heavy Metals in the Environment, (C. E. C. W. H. O.), pp. 553—556.

Winneke, G. (1982): Neuropsychological lstudies in children with elevated tooth lead concentrations. In *Rutter, M.* (ed.): Low Level Lead Exposure and Its Effect on Human Beings, John Wiley, New York.

Yule, W., Lansdown, R., I. B. Millar & M. A. Urbanowicz (1981): The relationship between blood lead concentrations intelligence and attainmet in a school population: A pilot study. Dev. Med. Chil. Neurol. *23*, 567—571.

Needleman, Herbert L, M. D.
Associate Professor
of Child Psychiatry and Pediatrics
University of Pittsburgh
Department of Psychiatry
125 DeSoto Street
Pittsburgh, PA 15213.

REPRODUCED AT GOVERNMENT EXPENSE